REMARKS

The Office Action of November 9, 2009 and the references cited therein have been carefully reviewed. Favorable reconsideration and allowance are respectfully requested.

I. Claim Status and Amendments

Claims 30, 32, and 34 presently appear in this case and stand rejected. No claims have been allowed.

By the present amendment, main claims 30, 32, and 34 have been amended, in a non-narrowing manner, to insert the statement of the preamble in the body of the claims. Other minor editorial and non-narrowing revisions have been made to the claims to better conform to US claim form and practice.

New dependent claims 60, 61, and 62 have been added that specify that the route of administration is intravenous injection, infusion, oral ingestion, or intraperitoneal injection. Support can be found throughout the general disclosure. See, for instance, the following sections in the corresponding patent application publication no. 20060269524: paragraph [0080]; paragraph [0087]; paragraph [0090]; Example 1, paragraphs [0084], [0087], [0090]; Example 2, paragraph [0098]; Example 8, paragraph [0112]; Example 9, paragraph [0114]; Example 10, paragraph [0118]; and Example 11, paragraph [0122].

No new matter has been added.

Claims 30, 32, 34, and 60-62 are pending upon entry of this amendment, and these claims define patentable subject matter warranting their allowance for the reasons discussed herein.

II. Priority Claim

Applicants note with appreciation the Examiner's acknowledgement of the priority claim and the receipt of Applicants' papers filed under § 119.

III. Anticipation Rejections

Claims 30, 32, and 34 have been rejected under 35 U.S.C. § 102(b) as being separately anticipated by Kawahara et al. (PG Pub No. US 2002/0037291 A1) or Murata et al. (US 6,348,201) for the reasons on pages 5-8 of the Office Action. These rejections are respectfully traversed.

To start, the claimed methods relate to the administration of a glycosphingolipid cell activator of specified formula to a mammal in order to activate NKT cells (claim 30), accelerate IL-4 production (claim 32), or accelerate IFN-γ production (claim 34). The claimed methods are characterized in that the glycolsphingolipid (hereinafter, referred to as GSL) is administered in such a manner to work as a ligand of CD1, thereby activating NKT cell. Thus activation of NKT cell results in the production of large amounts of IL-4 and IFN-γ, as shown in the application (see for instance, Example 1, starting at paragraph [0083]). It should be noted that the mechanism of the claimed methods is the same as that disclosed in Wu et al. (PNAS, vol.

102, no. 5., pp. 1351-1356 (Feb. 1, 2005))[1]. This mechanism of action can be recognized from Example 1 of the present specification, which discloses experiments utilizing CL11a, i.e., PE-labeled anti-NK1.1 antibodies (Example 1, paragraph [0087]) and shows that GSL activates NKT cells as measured by IL-4 and IFN-γ production.

To emphasize the above-noted features and for the sake of clarity, Applicants have amended main claims 30, 32, and 34 to positively recite (in the body of the claims) that the administering steps, respectively, results in: (i) activating NKT cells, (ii) accelerating IL-4 production, and (iii) accelerating IFN-γ production.

The cited references are silent with respect to activation of NKT cells, IL-4 production, and IFN-γ production. There is no disclosure or suggestion in the references that the methods disclosed therein would result in these effects, as required in claims 30, 32, and 34. The Examiner acknowledges this point when stating that the references "do not disclose that the glycosphingolipid in the method of the references activates NKT cells, IL-4 production, or IFN-γ production." Yet, the Examiner relies on a theory of inherency in making the rejections, as evident from the statements at lines 8-12 on page 6, and in the last paragraph on page 6 of the Action. At this

[1] Wu et al. was previously cited in the IDS of August 7, 2006 and in the Office Action of August 17, 2009. Wu et al. was published on February 1,

location, the Examiner cites to case law on inherency, when noting that the prior art method is "intended for administration to a mammal" and when stating that the prior art teaches the same or nearly the same method steps. The Examiner further states:

> However, whether the glycosphingolipid activates NKT cells, IL-4 production, or IFN- γ production or not, is considered a mere mechanism of action of the glycosphingolipid. The recitations "activating NKT cells," "accelerating IL-4 production," and "accelerating IFN-γ production," in the claim is considered to be merely a mechanism of the action of the application. Applicants' recitation of a new mechanism of action for the prior art method would not, by itself, distinguish the instant claims over the prior art teaching the same or nearly the same method steps. [Emphasis added.]

Accordingly, the Examiner argues that Applicants are merely reciting a new mechanism of action for the prior art method, which does not distinguish over the prior art, which teaches the same or nearly the same method steps. In other words, the Examiner appears to argue that the prior art methods "are the same or nearly the same" as the claimed methods, and thus, the prior art methods and the GSL disclosed therein would necessarily (i.e., inherently) have the same mechanism of action and produce the same result, as the claimed invention. The Examiner provides the same rationale for the rejection over Murata et al. Applicants respectfully disagree.

2005, which is after the priority date of February 19, 2004 of the present application, and thus it is not available as a reference against the claims.

The methods in the prior art references are not the same as the claimed methods. The cited references only contemplate external uses involving topical application of GSL to the skin for completely different purposes than the claimed method. By contrast, and as noted above, the methods of the claims do not contemplate external application. Instead, claims 30, 32, and 34 contemplate administering GSL internally, and to this end, the claims have been amended to positively recite (in the body of the claims) that the administering step, respectively, results in: (i) activating NKT cells, (ii) accelerating IL-4 production, and (iii) accelerating IFN-γ production. As such, the recited method steps of the claims require administering GSL in a manner (for example, by intravenous injection, infusion, oral ingestion, or intraperitoneal injection) to achieve this effect. For the reasons discussed herein, the prior methods involving external topical application are not believed capable of achieving this effect.

The Examiner's inherency argument is based on pure speculation, because there is not the remotest implication in either reference that GSL activates NKT cells, IL-4 production, or IFN-γ production, regardless as to whether GSL is administered externally for topical use as in the references or by internal use, such as injection. Moreover, reliance on inherency requires that the missing feature be necessarily present in the applied

reference. As stated in *Ex parte Levy*, 17 USPQ 2d 1461, 1463-64 (BPAI 1990):

> In relying on the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teaching of the applied prior art. [citations omitted: emphasis in the original]

Please also see *In re Robertson*, 49 USPQ2d 1949, 1951 (Fed. Cir. 1999):

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. [citations omitted]

See also the discussion at MPEP §2112, which discusses the case law and explains the requirements of a rejection based on inherency. MPEP §2112 states:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted)

In the instant case, the Examiner's inherency argument relies on the assumptions that GSL's have the same mechanism of action, and that the prior art method of external/topical application to the skin would necessarily produce the same mechanism of action with the same results of the claims. However, there is no reasonable certainty that these assumptions are correct. Certainly, no evidence or prior art teaching has been presented by the Office to support these assumptions. Indeed, for the reasons discussed herein, it is more than likely that they are not correct.

It does not necessarily follow that all GSL's have the same mechanism of action. Nor is there a reasonable certainty that topical application of GSL produces the same effects, as recited in the claims. Indeed, it is known that different kinds of GSL effectively work by different mechanisms of action, as evident by the disclosure in Krziwon et al. (Infection and Immunity, vol. 63, no. 8, pp. 2899-2905 (August 1995)), a copy of which is submitted herewith. In Krziwon's mechanism, GSL stimulates monocular cells or monocytes (Table 1 of Krziwon). It can be recognized from Fig. 2 of Krziwon that the mechanism disclosed in Krzion is distinctly different from that of the claimed invention. This is because the mechanism in Krziwon is effective for GSL-1, which corresponds to GSL-1 of the invention, but the mechanism in Krziwon is not effective for GSL-4A, which also corresponds to GSL-2 of the present invention. In contrast,

both GSL-1 and GSL-2 work as a ligand of CD1, thereby activating NKT cell (as shown in Example 1 of the present application). Thus, contrary to the position taken in the Office Action, it does not necessarily follow that the GSL in the method of the prior art references necessarily has the same mechanism of action with the same results, as required in the claims.

Furthermore, the differences in the objectives and the routes of administering GSL between the claimed method and the prior art methods also support the above conclusion.

Kawahara et al. and Murata et al. both disclose only an external composition for external/topical application to the skin or the head. Though Kawahara et al. briefly mentions pharmaceutical uses, Kawahara only discloses and exemplifies external cosmetic uses that are topically applied. See paragraphs [0037] to [0038] of Kawahara, which only disclose external cosmetic uses. The examples in Kawakara, as represented by Examples 2-21 on paragraphs [0078] to [0098], solely relate to external cosmetic uses, such as beauty skin milk, lotion, powder foundation, whitening powder, emollient cream, pre-shaving lotion, cleansing foam, lipstick, etc. Accordingly, Kawakara et al. only really discloses external uses, and never contemplates administering GSL internally for activation of NKT cells and accelerating IL-4 production and IFN-γ production.

Similarly, Murata et al. also relates only to topical cosmetic applications. Though Murata et al., at paragraph

[0001], mentions that GSL can be used for cosmetics and pharmaceuticals purposes, Murata et al. only discloses and exemplifies cosmetic uses in the Examples.

Based on the above, it is clear that Kawahara et al. and Murata et al. disclose cosmetic uses involving topical applications only for applying GLS on the skin or head. However, it is generally understood that topical application of a substance results in a local effect, as the substance is applied directly where its action is desired. It is further believed that topical administration to skin, as disclosed in the cited references, cannot achieve the results of claims.

In this regard, it is well-known that skin is damaged when an intercellular substance such as ceramide decreases. Kawahara et al. and/or Murata et al. use GSL as a supplement of this intercellular substance. GSL include ceramide, and therefore, GSL would work as alternative to the intercellular substance in skin and thus recover the damaged skin. By contrast, NKT activation is caused by directly acting on CD1, which is a completely different process as compared to use of GSL as a supplement of an intercellular substance, i.e., ceramide, to repair damaged skin.

Therefore, it is believed that topical administration to skin cannot achieve the results of the claims. As such, it does not necessarily follow that all GSL's have the same mechanism of action, and indeed, it is believed that this is the

case here. Nor is there a reasonable certainty that topical application of GSL produces the same effects, as recited in the claims. Consequently, the Examiner's inherency rejection fails, because the allegedly inherent features are not necessarily present in the teachings of the cited references. This effectively rebuts the Examiner's inherency argument. Thus, it is believed that the cited references cannot contemplate administering GSL internally, wherein it is used as a ligand of DC1 to activate NKT cells, to result in the production of large amounts of IL-4 and IFN-γ, as recited in the claims.

Contrary to the prior art teachings, the claimed invention does not contemplate external/topical application of GSL. Instead, the claimed invention contemplates administering GSL internally to accomplish: (i) activating NKT cells, (ii) accelerating IL-4 production, and (iii) accelerating IFN-γ production, as required in the claims. Again, claims 30, 32, and 34 have been amended to positively recite (in the body of the claims) that the administering step results in (i) activating NKT cells, (ii) accelerating IL-4 production, and/or (iii) accelerating IFN-γ production. Also, for the reasons discussed herein, it is believed that the NKT cell activation, IL-4 production, and IFN production do not involve the same mechanism of action of GSL, as disclosed in Kawahara et al. or Murata et al.

Given the above, it is respectfully submitted that the cited references fail to disclose the claimed method steps for administering GSL to achieve the desired effects recited in the claims. Thus, the rejections should fall, because Kawahara et al. and Murata et al., taken alone or even if combined, fail to disclose on each and every element of the claims, as required for anticipation under 34 USC §102(b). For these reasons, withdrawal of the rejections is requested.

Lastly, Applicants respectfully submit that Kawahara et al. and Murata et al. also fail to anticipate newly added claims 60, 61, and 62 that respectively depend on claims 30, 32, and 34, and further specify that the route of administration is intravenous injection, infusion, oral ingestion, or intraperitoneal injection. Again, the cited references only disclose topical/external application, which is not the same as, nor is it suggestive of, administering GSL by intravenous injection, infusion, oral ingestion, or intraperitoneal injection. Thus, the rejections do not and should not be applied to new claims 60-62.

IV. Obviousness Rejection

Claims 30, 32, and 34 have been rejected under 35 USC §103(a) as being unpatentable over Kawahara (US 5,672,693) (hereinafter referred to as the '693 patent) as evidenced by Laloux et al. (The Journal of Immunology, vol. 168, pp. 3251-3258, 2002), in view of Nicoara et al. (Timisoara Medical

Journal, vol. 53, nos. 3-4, pp. 303-307, 2003) for the reasons on pages 9-12. This rejection is respectfully traversed.

The obviousness rejection should fall, because the cited prior art references fail to teach, suggest or make obvious all of the features of claims 30, 32, and 34, as required to support a *prima facie* case of obviousness.

The '693 patent to Kawahara is directed to activation of B cells (column 12) *in vitro*. However, nowhere does the patent disclose or suggest administering GSL internally to result in: (i) activating NKT cells, (ii) accelerating IL-4 production, and (iii) accelerating IFN-γ production. The Examiner acknowledges this point in the middle of page 10 of the Action.

Further, it should be noted that in the '693 patent, GSL does not directly work with CD1d. This is because the '693 patent discloses that "the glycoliopid of the present invention possesses a B cell mitogen activity" (See Column 7, lines 45-54 of Kawahara, the '693 patent). That is, the '693 patent discloses that a certain kind of GSL works as mitogen of B cell. It is well-known that mitogen encourages a cell such as a B cell or a T cell to commence cell division, thereby triggering mitosis. It is also well-known that mitogen acts <u>on</u> B cells or T cells, as evidenced by the submitted copy of the Wikipedia definition of mitogen. Based on this, the skilled person would have believed that, in the '693 patent, GSL acts on B cell, and therefore, GSL cannot directly work with CD1d.

The Examiner turns to the secondary references of Laloux et al. and Nicoara et al. to remedy the above-noted deficiencies in the '693 patent. Specifically, on page 10, the Examiner states that Laloux et al. discloses that NKT cells are present in mice spleen, which also produces IFN-γ and IL-4. However, the mere fact that NKT cells are present in an *in vitro* culture of mice spleen cells does not necessarily mean, nor is it a suggestion, that GSL activates said cells. No teaching has been presented to support the Examiner's position. Thus, Applicants fail to see how the combination of the '693 patent and Laloux et al. suggests that GSL activates NKT cells, and accelerates IL-4 production and IFN-γ production, let alone a method of administering GSL internally to accomplish such. Indeed, it is respectfully submitted that the combination does not suggest this.

Furthermore, neither the '693 patent, nor Laloux et al., teach *in vivo* administration of GSL to a mammal for any purpose, let alone for (i) activating NKT cells, (ii) accelerating IL-4 production, and (iii) accelerating IFN-γ production. The Examiner relies on the general review of Nicoara et al. for teaching that immunomodulators have been used to stimulate the defense mechanisms for treatment of viral, bacterial, parasitic and fungal diseases. However, Nicoara et al. mentions nothing with respect to the ability of GSL to accomplish this. Thus, Nicoara et al. does not remedy the above-

noted deficiencies in the '693 patent and Laloux et al. There is no basis for modifying the references to arrive at each and every element the claimed invention.

Thus, Applicants respectfully submit that the *in vitro* use in the '693 patent for B cell activation, even if combined with Laloux et al. and Nicoara et al., does not disclose or suggest each and every element of the claimed invention. For these reasons, Applicants respectfully submit that the obviousness rejection is untenable and should be withdrawn.

V Double Patenting Rejection

Claims 30, 32, and 34 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of US 6,348,201 to Murata et al. for the reasons on pages 9-12.

Murata et al. is the same reference cited in the above anticipation. Accordingly, Applicants respectfully traverse the obviousness-type double patenting rejection for the same reasons (which arguments are reiterated herein by reference) set forth previously with respect to the anticipation rejection over Murata et al.

Again, Murata et al. discloses only an external composition for topical application on the skin. Murata et al. is silent with respect to activation of NKT cells, IL-4 production, and IFN-γ production. By contrast, main claims 30, 32, and 34 require *in vivo* administering in a manner to activate

NKT cells, accelerate IL-4 production, and accelerate IFN-γ production. There is no suggestion or rationale in the reference itself or in the Office Action to change the topical application in Murata et al. to injection. Nor is there any reasonable basis to suggest that, by making this change, it would result in activation of NKT cells and acceleration in IL-4 production and IFN-γ production

For the same reasons set forth above and immediately herein, Murata et al. cannot render obvious the claims. Thus, the rejection should be withdrawn.

VI. Conclusion

Having addressed all the outstanding issues, this paper is believed to be fully responsive to the Office Action. It is respectfully submitted that the claims are in condition for allowance, and favorable action thereon is requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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APPENDIX:

The Appendix includes the following item(s):

- Krziwon et al. (Infection and Immunity, vol. 63, no. 8, pp. 2899-2905 (August 1995));

- copy of Wikipedia definition of mitogen.